METHODS OF THERAPEUTIC MONITORING OF PHENYLACETIC ACID PRODRUGS

RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Application No. 61/636,256, filed Apr. 20, 2012, the disclosure of which is incorporated by reference herein in its entirety, including drawings.

BACKGROUND

Nitrogen retention disorders associated with elevated ammonia levels include urea cycle disorders (UCDs), hepatic encephalopathy (HE), and advanced kidney disease or kidney failure, often referred to as end-stage renal disease (ESRD).

UCDs include several inherited deficiencies of enzymes or transporters necessary for the synthesis of urea from ammonia, including enzymes involved in the urea cycle. The urea cycle is depicted in FIG. **1**, which also illustrates how certain ammonia-scavenging drugs act to assist in elimination of excessive ammonia. With reference to FIG. **1**, N-acetyl glutamine synthetase (NAGS)-derived N-acetylglutamate binds to carbamyl phosphate synthetase (CPS), which activates CPS and results in the conversion of ammonia and bicarbonate to carbamyl phosphate. In turn, carbamyl phosphate reacts with ornithine to produce citrulline in a reaction mediated by ornithine transcarbamylase (OTC). A second molecule of waste nitrogen is incorporated into the urea cycle in the next reaction, mediated by arginosuccinate synthetase (ASS), in which citrulline is condensed with aspartic acid to form argininosuccinic acid. Argininosuccinic acid is cleaved by argininosuccinic lyase (ASL) to produce arginine and fumarate. In the final reaction of the urea cycle, arginase (ARG) cleaves arginine to produce ornithine and urea. Of the two atoms of nitrogen incorporated into urea, one originates from free ammonia (NH_4^+) and the other from aspartate. UCD individuals born with no meaningful residual urea synthetic capacity typically present in the first few days of life (neonatal presentation). Individuals with residual function typically present later in childhood or even in adulthood, and symptoms may be precipitated by increased dietary protein or physiological stress (e.g., intercurrent illness). For UCD patients, lowering blood ammonia is the cornerstone of treatment.

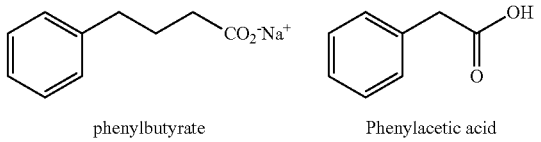
HE refers to a spectrum of neurologic signs and symptoms believed to result from hyperammonemia, which frequently occur in subjects with cirrhosis or certain other types of liver disease. HE is a common manifestation of clinically decompensated liver disease and most commonly results from liver cirrhosis with diverse etiologies that include excessive alcohol use, hepatitis B or C virus infection, autoimmune liver disease, or chronic cholestatic disorders such as primary biliary cirrhosis. Patients with HE typically show altered mental status ranging from subtle changes to coma, features similar to patients with UCDs. It is believed that an increase in blood ammonia due to dysfunctional liver in detoxifying dietary protein is the main pathophysiology associated with HE (Ong 2003).

ESRD results from a variety of causes including diabetes, hypertension, and hereditary disorders. ESRD is manifested by accumulation in the bloodstream of substances normally excreted in the urine, including but not limited to urea and creatinine. This accumulation in the bloodstream of substances, including toxins, normally excreted in the urine is

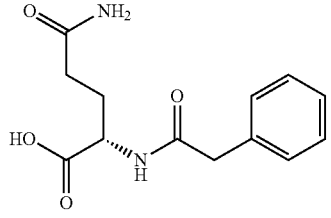
generally believed to result in the clinical manifestations of ESRD, sometimes referred to also as uremia or uremic syndrome. ESRD is ordinarily treated by dialysis or kidney transplantation. To the extent that urea, per se, contributes to these manifestations and that administration of a phenylacetic (PAA) prodrug may decrease synthesis of urea (see, e.g., Brusilow 1993) and hence lower blood urea concentration, PAA prodrug administration may be beneficial for patients with ESRD.

Subjects with nitrogen retention disorders whose ammonia levels and/or symptoms are not adequately controlled by dietary restriction of protein and/or dietary supplements are generally treated with nitrogen scavenging agents such as sodium phenylbutyrate (NaPBA, approved in the United States as BUPHENYL® and in Europe as AMMONAPS®), sodium benzoate, or a combination of sodium phenylacetate and sodium benzoate (AMMONUL®). These are often referred to as alternate pathway drugs because they provide the body with an alternate pathway to urea for excretion of waste nitrogen (Brusilow 1980; Brusilow 1991). NaPBA is a PAA prodrug. Another nitrogen scavenging drug currently in development for the treatment of nitrogen retention disorders is glyceryl tri-[4-phenylbutyrate] (HPN-100), which is described in U.S. Pat. No. 5,968,979. HPN-100, which is commonly referred to as GT4P or glycerol PBA, is a prodrug of PBA and a pre-prodrug of PAA. The difference between HPN-100 and NaPBA with respect to metabolism is that HPN-100 is a triglyceride and requires digestion, presumably by pancreatic lipases, to release PBA (McGuire 2010), while NaPBA is a salt and is readily hydrolyzed after absorption to release PBA.

HPN-100 and NaPBA share the same general mechanism of action: PBA is converted to PAA via beta oxidation, and PAA is conjugated enzymatically with glutamine to form phenylacetylglutamine (PAGN), which is excreted in the urine. The structures of PBA, PAA, and PAGN are set forth below:



phenylbutyrate Phenylacetic acid



Phenylacetylglutamine

The clinical benefit of NaPBA and HPN-100 with regard to nitrogen retention disorders derives from the ability of PAGN to effectively replace urea as a vehicle for waste nitrogen excretion and/or to reduce the need for urea synthesis (Brusilow 1991; Brusilow 1993). Because each glutamine contains two molecules of nitrogen, the body rids itself of two waste nitrogen atoms for every molecule of PAGN excreted in the urine. Therefore, two equivalents of nitrogen are removed for each mole of PAA converted to PAGN. PAGN represents the predominant terminal metabo-